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Molecular Studies of Translocations and Trisomy Involving Chromosome 13

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Twenty-four cases of trisomy 13 and one case with disomy 13, but a de novo dic(13,13)(p12p12) chromosome, were examined with molecular markers to determine the origin of the extra (or rearranged) chromosome. Twenty-one of 23 informative patients were consistent with a maternal origin of the extra chromosome. Lack of a third allele at any locus in both paternal origin cases indicate a somatic duplication of the paternal chromosome occurred.

Five cases had translocation trisomy: one de novo rob(13q14q), one paternally derived rob(13q14q), two de novo t(13q13q), and one mosaic de novo t(13q13q)/r(13). The patient with a paternal rob(13q14q) had a maternal meiotic origin of the trisomy; thus, the paternal inheritance of the translocation chromosome was purely coincidental. Since there is not a significantly increased risk for unbalanced offspring of a t(13q14q) carrier and most trisomies are maternal in origin, this result should not be surprising; however, it illustrates that one cannot infer the origin of translocation trisomy based on parental origin of the translocation. Lack of a third allele at any locus in one of the three t(13q13q) cases indicates that it was most likely an isochromosome of postmeiotic origin, whereas the other two cases showed evidence of recombination. One balanced (nontrisomic) case with a nonmosaic 45,−13,−13,+t(13;13) karyotype was also investigated and was determined to be a somatic Robertsonian translocation between the maternal and paternal homologues, as has been found for all balanced homologous Robertsonian translocations so far investigated. Thus, it is also incorrect to assume in de novo translocation cases that the two involved chromosomes are even from the same parent. Despite a maternal origin of the trisomy, we cannot therefore infer anything about the parental origin of the chromosomes 13 and 14 involved in the translocation in the de novo t(13q14q) case nor for the two t(13;13) chromosomes showing a meiotic origin of the trisomy. © 1996 Wiley-Liss, Inc.

KEY WORDS: trisomy 13, nondisjunction, Robertsonian translocation, isochromosome

INTRODUCTION

DNA polymorphisms have proven useful to demonstrate the origin of nondisjunction for trisomy 13 [Hassold et al., 1987; Zaragoza et al., 1994], trisomy 14 and 15 [Zaragoza et al., 1994], trisomy 16 [Hassold et al., 1991], trisomy 18 [Fisher et al., 1993; Nöthen et al., 1993; Ya-gang et al., 1993], trisomy 21 [Antonarakis et al., 1991, 1993; Lorber et al., 1992; Sherman et al., 1991, 1994] and uniparental disomy 15 [Robinson et al., 1993a]. However, only for trisomy 18 and 21 are there large numbers (more than 50) of patients for which origin has been determined. Most autosomal trisomy cases studied so far arose through a maternal meiosis I segregation error. Only a small number of cases of paternal origin have been identified and these were primarily due to meiosis II or mitotic errors.

An interesting characteristic of trisomies involving acrocentric chromosomes is the frequent observation of "translocation trisomy," i.e., that associated with isochromosomes or Robertsonian translocations. Most translocations found in association with trisomy 13 are de novo, and the risk of unbalanced outcome is very low for both male and female carriers of rob(13q14q), the most common Robertsonian translocation [Hamerton, 1970; Boué and Gallano, 1984; Daniel et al., 1989; Therman and Susman, 1993]. This is in contrast to Robertsonian translocations involving chromosome 21 for which carrier women are at increased risk (greater

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than 10%) of unbalanced offspring, especially trisomy 21 [Boué and Gallano, 1984].

We hereby present molecular investigations on 24 cases of trisomy 13, two of which were mosaic. Cytogenetic studies were not performed in case 30 or 34, but the clinical diagnosis of trisomy 13 was confirmed by molecular analysis showing three different chromosome 13 alleles. Five of these cases showed translocation trisomy and were included with the aim to determine how the translocations have arisen, and how such translocations lead to aneuploidy.

PATIENTS AND METHODS

Patients were ascertained through trisomy 13 phenotype and consisted of fetuses and liveborn infants. A list of the propositi and their cytogenetic karyotypes is given in Table I. Five cases had translocation trisomy: one de novo rob(13q14q), one paternally derived rob(13q14q), two de novo t(13q13q), and one mosaic de novo t(13q13q)/r(13). The mosaic ratio in this last patient (T13-22) was determined to be (in lymphocytes): 46,XY,−13,+t(13;13)(p11;q14) 50% (25 mitoses)/46,XY, r(13) 48% (24 mitoses), and 47,XY,−13,+t(13;13) (p11;q14),r(13) 2% (1 mitosis). In skin, 90% of mitoses showed the 46,−13,+t(13q13q) cell line. Two additional cases (T13-1 and T13-25) were mosaic with a disomic cell line, and molecular results on these patients are also being published elsewhere as part of a study on mosaicism [Robinson et al., 1995]. For comparison of parental ages, a Swiss population control group was used as described previously [Robinson et al., 1993b].

Molecular analysis in all patients and their parents was performed using polymerase chain reaction (PCR) amplification of microsatellite polymorphisms. The following loci were examined: D13S115, D13S221, D13S162, D13S170, D13S71, D13S158, D13S173, D13S118, D13S137. Information on primers is available from the Genome Data Base. Additional information on map location is available from NIH/Ceph Collaborative Mapping Group [1992], and Weissenbach et al. [1992]. All primers were obtained from Research Genetics Inc.

PCR amplification was performed on a Perkin Elmer Thermocycler with 30–32 cycles of 1 minute at 94°C denaturation, 1 minute at 55–57°C annealing and 1–2 minutes at 72°C extension temperatures; 0.5–3 μl of reaction was mixed with an equal volume of urea loading buffer (42% urea, 0.1% xylene cyanol, 0.1% bromphenol blue and 0.1% of 0.5 M EDTA) and directly loaded onto a 0.4-mm-thick 6% polyacrylamide/50% urea gel. Visualization of bands was done either by including ^{32}P-labelled cytosine in the PCR and exposure of the gel to X-ray film, or usually by silver staining of the gels.

The presence of 3 alleles at one or more loci indicates that the trisomy originated as a meiotic error. Parental origin could be determined when 2 of the 3 alleles could have come from only one parent. Parental origin of the extra chromosome could also be inferred when 2 alleles were present if a consistent difference in intensity of the 2 alleles was observed. The sex-averaged chromosome 13 map has been estimated as 164 cM [Bowcock, 1993] or more than 200 cM [NIH/Ceph Collaborative Mapping Group, 1992; Buetow et al., 1994]. Therefore, an average of 3–4 chiasma occur for chromosome 13 during meiosis (50 cM corresponds to 1 chiasma). Therefore, it is normal to observe regions of the "nondisjoined" chromosome pair which have retained parent of origin heterozygosity at some loci and show

TABLE I. Summary of 23 Trisomy 13 Cases Plus One Balanced t(13;13) Case

Case		Mat. age[a]	Pat. age[a]	Karyotype	Molecular results
T13-1	liveborn	NA[b]	NA	46/47,+13	mat-meiotic
T13-2	liveborn	32	36	46,−14,+rob(13q14q)	mat-meiotic
T13-3	fetus	39	42	47,+13	mat-meiotic
T13-4	fetus	32	41	47,+13	mat-meiotic
T13-5	liveborn	25	NA	46,−14,+rob(13q14q)pat	mat-meiotic
T13-6	liveborn	26	28	47,+13	mat-somatic
T13-7	liveborn	28	32	47,+13	mat-meiotic
T13-8	liveborn	31	36	47,+13	mat-somatic
T13-9	liveborn	39	44	47,+13	mat-meiotic
T13-10	fetus	29	32	47,+13	pat-somatic
T13-11	fetus	NA	NA	47,+13	mat-meiotic
T13-15	fetus	29	NA	47,+13	mat-meiotic
T13-17	fetus	37	32	47,+13	mat-meiotic
T13-22	liveborn	30	35	46,−13,+i(13q)/46,−13,+r13	somatic?
T13-23	liveborn	33	33	47,+13	mat-meiotic
T13-24	fetus	33	NA	47,+13	mat?-meiotic
T13-25	liveborn	33	35	46/47,+13	mat-meiotic
T13-26	fetus	41	41	47,+13	mat-meiotic
T13-27	liveborn	30	35	46,−13,+i(13q)	mat-meiotic
T13-28	liveborn	NA	NA	46,−13,+i(13q)	mat-meiotic
T13-30	liveborn	29	32	not done	mat-meiotic
T13-31	liveborn	27	NA	47,+13	pat-somatic
T13-34	liveborn	30	35	not done	mat-meiotic
T13-35	liveborn	30	28	47,+13	mat-meiotic
t(13p;13p)	normal adult	39	39	45, dic(13;13)(p12p12)	mat/pat-somatic

[a]Mat, maternal; pat, paternal.
[b]NA, not available.

reduction to homozygosity at others; however, it is unlikely, using markers which span the chromosome pair, that no locus would retain the parent-of-origin heterozygosity. It is therefore assumed that when all markers on the chromosome pair show reduction to homozygosity that this is most likely because the extra chromosome has arisen by a postzygotic duplication mechanism [Antonarakis et al., 1993; Robinson et al., 1993a; MacDonald et al., 1994]. From our experience with chromosome 15 uniparental disomy, even just two randomly chosen informative markers have less than 5% probability of both showing reduction to homozygosity if the error is meiotic (unpublished results). In order to distinguish between a meiosis I and meiosis II origin, centromeric markers are necessary. Markers mapping close to the centromere can be used with some error; however, D13S115 is the closest marker at approximately 26 cM from the centromere [interpolating from Buetow et al., 1994; Matise et al., 1994], which would result in 20–40% error rate and is too high to be useful in this regard.

RESULTS

The inferred origin of the extra chromosome and molecular results are given on all patients in Tables I and II. A maternal origin of the extra chromosome could be shown in 19 of 21 fully informative cases, including case T13-5 who had inherited a rob(13q14q) from her father; only two cases (10 and 31) had a paternal origin of the extra chromosome. Two additional cases (11 and 24) were also consistent with a maternal origin at all markers; however, paternal DNA was not available and a maternal origin could not be unambiguously proven. In the remaining t(13q13q)/r(13) mosaic case, parental origin could not be assigned as a third allele was not observed at any locus and a clear difference in intensity of alleles was not observed.

In most cases (16 of 24), at least one locus showed presence of 3 alleles, proving a meiotic origin. In 3 additional cases (2, 27, and 28), presence of parent-of-origin heterozygosity could be inferred by dosage. PCR of the informative marker in these cases was repeated to exclude that the dosage difference was not just an experimental artifact. In 5 cases, including both of paternal origin, 5 or more informative markers showed reduction to homozygosity indicative of a somatic origin of the extra chromosome 13.

Although parental origin could not be determined in the t(13;13)/r(13) mosaic case, since the frequency of trisomic cells was about 50%, a faint third allele, if present, should have been observable. Both parents were heterozygous at most of the loci; therefore, the lack of a "third allele" makes it likely that this case was postmeiotic in origin. All 3 translocation t(13;13) chromosomes associated with trisomy showed reduction to homozygosity of markers closest to the centromere indicative of isochromosomes. Most t(21;21) chromosomes associated with trisomy 21 have also been shown to be isochromosomes [Shaffer et al., 1993]. However, the probability of misclassification using D13S115 can be as high as 28% [Shaffer et al., 1994]. Therefore, we cannot be certain whether cases 27 and 28 are isochromosomes of prezygotic origin or Robertsonian translocations of either pre- or postzygotic origin.

TABLE II. Molecular Results for 23 Trisomy 13 Cases[a]

Case:	1	2	3	4	5	7	9	11	15	17	23	24	25	26	27	28	30	34	35	6	8	10	22	31
Marker	mat	mat	mat	mat	mat	mat	mat	mat	mat	mat	mat	mat	mat	mat	mat	mat	mat	mat	mat	mat	mat	pat	?	pat
D13S115	N	*	*	*	R	N	*	*	*	N	*	N	*			R			N	*	R	R		
D13S221	R	*	N	*	R	N	*	*	N	R	*	N	N		*	N	N	*	N	*	R	R	R	R
D13S118																	N	N					R	R
D13S162	N	N	N	N	N	N	N	N	N	*	N	R	N	N	*		*	*	*	R	R	R	R	R
D13S170	N	*	R	*	R	N	N	N	*	N	N	R	N		R	R				R	*	R	R	R
D13S71	*	*	N	*	R	*	N	*	*	N	*	*	*	*	R	R				R	R	*	*	
D13S158	N	*	*	N	N	N	*	R	N	N	N	*	*	N	*	*	*	*	N	*	R	R	R	*
D13S173	N	*	R	R	N	*		*	N	N	*		*		*		*			R	R	R	R	R
D13S124	R	*	*	*	R	*	*	*	*	N	N	*	*	*	N	R				R	*	R	*	*

[a]Parental origin of the trisomy is given under the case number. Each marker is designated N if parent of origin heterozygosity was nonreduced in the proband; R if reduced to homozygosity, and * if the results were uninformative. The last five cases show reduction to homozygosity for all informative markers. In addition, marker D13S137 (located between D13S221 and D13S162) was typed in case 31 and both also confirmed a paternal origin and reduction of paternal heterozygosity to homozygosity.

In addition to the 24 trisomy 13 cases, one non-trisomic case with a balanced t(13;13) karyotype was investigated with molecular markers and shown to have both maternal and paternal inheritance. Markers D13S221, D13S162, D13S170, and D13S173 showed maternal and paternal inheritance. This indicates that this was a Robertsonian translocation occurring after zygote formation, and is similar to our previous findings on homologous Robertsonian translocations for chromosomes 14, 15, 21, and 22 [Robinson et al., 1994].

Both mean maternal and paternal age at birth was significantly increased in trisomy 13 cases as compared with Swiss population controls [Robinson et al., 1993b] (Table III). The increase was even greater when only maternal meiotic cases were considered.

DISCUSSION

Origin of Trisomy

In the present study, most cases (20 of 22 informative) were consistent with a maternal origin of the extra chromosome, and a meiotic origin could be shown in 18 of these cases. In contrast, both paternal cases were consistent with a somatic origin based on complete homozygosity. A predominantly maternal origin of the extra chromosome in trisomy 13 was also reported by Hassold et al. [1987] primarily based on analysis of cytogenetic heteromorphisms. Studies of the origin of trisomy 21 have been shown to have a significant error rate when origin is determined by cytogenetic rather than molecular means [Lorber et al., 1992; Antonarakis et al., 1991]. However, further molecular studies in seven of these trisomy 13 patients plus additional new cases confirmed that 22 of 25 cases were maternal in origin, and all were due to a meiotic error except one maternal case [Zaragoza et al., 1994]. The observed frequency of paternal origin of free trisomy 13 in the present study of 2 in 19 (11%) is similar to the 3 in 25 (12%) observed by Zaragoza et al., [1994].

Most cases of meiotic origin (9 of 17 with two or more informative markers) showed evidence of recombination despite the relatively small number of informative markers for many cases. This would seem to indicate that complete lack of chromosome pairing is not a major factor leading to nondisjunction of chromosome 13, as has also been concluded for chromosomes 15 [Robinson et al., 1993a], 16 [Hassold et al., 1991], and 21 [Sherman et al., 1994].

Translocation Trisomy

It is tempting to assume in studies of translocation trisomy that the parental origin of the translocation chromosome (in either de novo or familial cases) is the same as the parental origin of the trisomy. However, a maternal meiotic origin of the extra chromosome 13 was observed in the present case 5 who had coincidentally also inherited a paternally derived translocation t(13q14q) from her father. Of 230 amniocenteses performed on pregnancies of a t(13q14q) carrier parent, no unbalanced results were obtained [Boué and Gallano, 1984]. If there is not a significantly increased risk for unbalanced offspring of a t(13q14q) carrier, and most trisomies are maternal in origin, this result in the present t(13q14q) case should not be surprising.

In addition, there is an absence of unbalanced offspring from male t(14;21) translocation carriers, whereas female t(14;21) carriers have 10% risk of unbalanced offspring, especially trisomy 21 [Boué and Gallano, 1984]. The risk of unbalanced offspring for male carriers of all nonhomologous Robertsonian translocations is low and is likely to be due to strong selective disadvantage of unbalanced products of male meiosis. It would be particularly interesting to determine molecularly if the few other observations reported of a trisomic offspring of such male Robertsonian translocation carriers likewise showed a maternal origin of the extra chromosome.

The molecular results indicated that two of the three 13;13 translocations were of maternal origin with inheritance of two different maternal alleles. The third case showed complete homozygosity and was likely an isochromosome of postzygotic origin. Molecular studies of four similar cases were reported recently and three of the four cases were determined to be completely homozygous isochromosomes [Shaffer et al., 1994]. The origin of the trisomy has been determined in a total of 7 t(13;13) trisomy 13 cases using molecular polymorphisms, four of which have been maternal and three paternal in origin [present study (2 cases); Hassold et al., 1987 (1 case); Shaffer et al., 1994 (4 cases)]. Similarly, studies on the origin of t(21;21) chromosomes ascertained through trisomy 21 indicate that these are usually isochromosomes, and an approximately equal ratio of maternally to paternally derived cases was found [Grasso et al., 1989; Antonarakis et al., 1990; Shaffer et al., 1991, 1993]. Most isochromosomes have shown no evidence of recombination, consistent with a postmeiotic origin. Complete homozygosity of an isochromosome could occur if isochromosome formation occurred in meiosis II following an achiasmate meiosis I; however, the two events are expected to be independent, and are unlikely to be a mechanism that would account for most such isochromosomes.

In addition, the present balanced t(13;13) case, along with results from a previous study, confirm that Robert-

TABLE III. Mean Paternal Ages at Birth for Trisomy 13 Cases Compared With Swiss Population Controls

	Maternal age	Paternal age
Parental age all (n = 19, 16)	31.5*	35.5*
Maternal meiotic only (n = 15, 11)	32.4*	36.6*
Somatic (n = 6, 5)	30.3	34.0
Swiss control (n = 125, 125)	29.0	31.0

*$P < 0.01$; Student's t-test.

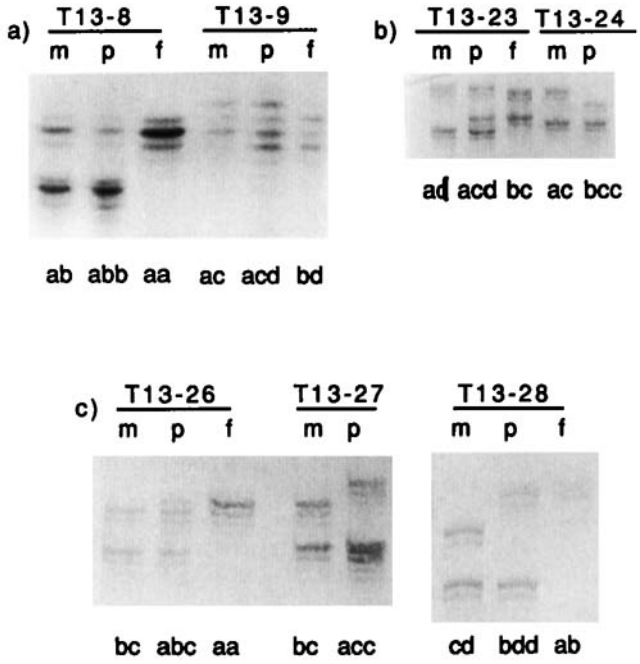

Fig. 1. **a:** Results for D13S71. Patient 8 has two copies of the maternal allele b; allele a was presumably inherited from the father. Patient 9 has three alleles, two of which must have come from the mother. **b** and **c:** D13S162. T13-23 and T13-26 have inherited two different maternal and one paternal allele. Cases T13-24, T13-27, T13-28 each have inherited only one of the two maternal alleles at this locus but at greater intensity. m, mother; p, patient; f, father.

sonian translocations may also commonly arise by a postzygotic event [Robinson et al., 1994]. Therefore, it would also be incorrect to assume in de novo translocation cases that the two involved chromosomes are even from the same parent. Thus, we cannot infer anything about the origin of the chromosomes 13 and 14 involved in the case with de novo t(13;14) plus a maternally derived trisomy 13. In addition, we cannot exclude that the two t(13;13) trisomy cases showing evidence of recombination were not postzygotic Robertsonian translocations in a trisomy 13 conceptus. The presence of homozygosity near the centromere would be compatible with either an isochromosome or a Robertsonian translocation following a meiosis II nondisjunction. Parental age was not available for one of these cases, but was above average in case 27.

In summary, the present results indicating a primarily maternal origin of trisomy 13 are concordant with similar molecular studies for other chromosomes. Approximately 12% of cases are paternal in origin; however, these may be primarily postzygotic mitotic errors. Studies of homologous translocations and translocation trisomy illustrate the difficulties of basing conclusions on origin of a chromosome aberration on the basis of cytogenetic evidence alone. It was often assumed that most Robertsonian translocations were meiotic in origin until recent molecular investigations proved this may not always, or even usually, be the case. It is also often assumed that the origin of a translocation, when associated with a trisomy, is the same as the origin of the trisomy. This is not always the case and caution must be used when indirectly inferring the origin of cytogenetic aberrations.

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